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**Abstract:** Primary cutaneous marginal zone lymphoma (PCMZL) is one of the most common cutaneous B-cell lymphomas. It affects mostly patients in their fourth decade and manifests with multifocal nodules mostly on the arms and upper trunk in more than half of the patients. PCMZL is, however, rare in children and adolescents, with only 20 cases reported in patients aged 20 and younger. The authors present 3 cases of PCMZL in teenagers. The patients were 2 girls aged 18 and 13 and a 17-year-old boy. Two patients presented with multiple lesions involving various anatomic sites, whereas in 1 patient, 2 small closely opposed papules on the abdomen were seen. Histopathologically, the characteristic appearance of PCMZL was found in 3 of 4 specimens, with nodular infiltrates composed of small lymphocytes in the interfollicular compartment, reactive germinal centers, and plasma cells in small clusters mainly at the periphery of the infiltrates, whereas 1 specimen showed a dense lymphocytic infiltrate with small granulomas. Clonality was demonstrated by monotypic immunoglobulin light chain expression and/or monoclonal rearrangement of the immunoglobulin heavy chain genes. No *Borrelia burgdorferi* was identified on serology or by polymerase chain reaction in any of the cases. Treatment included excision or administration of antibiotics with complete remission in all the 3 patients indicating that PCMZL in children and young adolescents follows the same indolent course with a tendency for recurrences, but excellent prognosis as in adults. The pertinent literature on PCZL in childhood and adolescence is reviewed.

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# Primary Cutaneous Marginal Zone Lymphoma in Children: A Report of 3 Cases and Review of the Literature

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**Abstract:** Primary cutaneous marginal zone lymphoma (PCMZL) is one of the most common cutaneous B-cell lymphomas. It affects mostly patients in their fourth decade and manifests with multifocal nodules mostly on the arms and upper trunk in more than half of the patients. PCMZL is, however, rare in children and adolescents, with only 20 cases reported in patients aged 20 and younger. The authors present 3 cases of PCMZL in teenagers. The patients were 2 girls aged 18 and 13 and a 17-year-old boy. Two patients presented with multiple lesions involving various anatomic sites, whereas in 1 patient, 2 small closely opposed papules on the abdomen were seen. Histopathologically, the characteristic appearance of PCMZL was found in 3 of 4 specimens, with nodular infiltrates composed of small lymphocytes in the interfollicular compartment, reactive germinal centers, and plasma cells in small clusters mainly at the periphery of the infiltrates, whereas 1 specimen showed a dense lymphocytic infiltrate with small granulomas. Clonality was demonstrated by monotypic immunoglobulin light chain expression and/or monoclonal rearrangement of the immunoglobulin heavy chain genes. No *Borrelia burgdorferi* was identified on serology or by polymerase chain reaction in any of the cases. Treatment included excision or administration of antibiotics with complete remission in all the 3 patients indicating that PCMZL in children and young adolescents follows the same indolent course with a tendency for recurrences, but excellent prognosis as in adults. The pertinent literature on PCZL in childhood and adolescence is reviewed.

**Key Words:** cutaneous lymphoma, marginal zone lymphoma, B-cell, childhood, adolescence, juvenile, pediatric, MALT, SALT

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## INTRODUCTION

Primary cutaneous marginal zone lymphoma (PCMZL) represents an indolent B-cell lymphoma composed of small B cells, marginal zone cells, lymphoplasmacytoid cells, and

mature plasma cells.<sup>1,2</sup> It affects mostly patients in their fourth decade and usually manifests with multifocal nodular lesions (up to 3 cm), most commonly located on the trunk and arms.<sup>3,4</sup> PCMZL is histologically characterized by dermal confluent nodular lymphocytic infiltrates composed of small lymphocytes, lymphoplasmacytoid cells, mature plasma cells, and reactive germinal centers with tingible body macrophages.<sup>5</sup> Predominance of monocytoid B cells instead of lymphoplasmacytic cells or plasma cells is occasionally seen.<sup>6</sup> PCMZL is rare in children and adolescents with only 20 cases reported in patients aged 20 and younger. Here we present 3 cases of pediatric PCMZL and review the previously published cases.

## MATERIALS AND METHODS

Three patients with PCMZL are the subjects of this report. Four biopsies were available for histopathological and molecular analysis. In all cases, routine light microscopy, immunohistochemical studies, and molecular biologic studies (IgH rearrangements) were performed.<sup>7</sup>

## RESULTS

### Clinical Data

The main features are summarized in Table 1. The patients were 2 teenager girls aged 13 and 18 years and a 17-year-old male patient. Two patients presented with multiple lesions involving various anatomic sites on the arms, the upper trunk, and the face (patients 1 and 3), whereas in 1 patient, 2 small closely opposed papules were present on the lower abdomen (patient 2) (Figs. 1, 2). The history was unremarkable concerning other skin diseases and autoimmune disorders. The male patient (patient 3) was known to have been taking methylphenidate for attention-deficit hyperactivity syndrome for 2 years before the occurrence of PCMZL. Remarkably, on withdrawal of the medicine, some of the lesions spontaneously regressed. Surgical excision of at least one of the lesions was performed in all patients. In patient 3, 2 of the lesions were treated with intralesionally applied interferon alpha (3 injections of 3 Mio IU per week) resulting in complete remission. In patient 1, treatment with doxycycline (100 mg twice per day for 14 days) resulted in partial regression of the lesions; during the course of the disease, additional nodules appeared on both arms and the back. At the last follow-up examination, she was alive with disease (Figs. 1, 2).

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The authors declare no conflicts of interest.

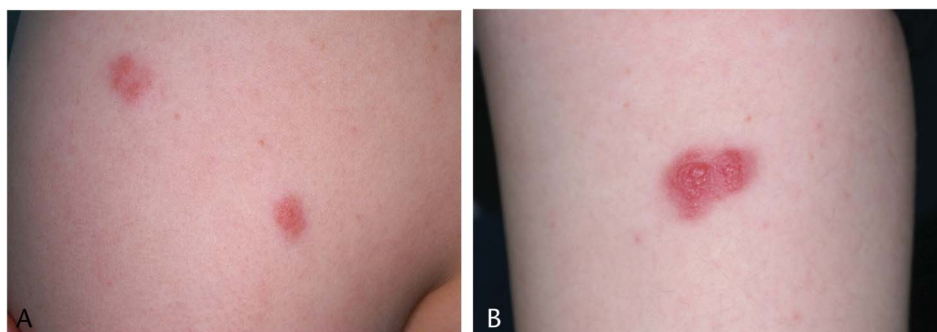
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**TABLE 1.** Clinicopathological Features of 3 Pediatric Patients With Primary Cutaneous Marginal Zone Lymphoma

Case	Age/Sex	Clinical Features	Clonality ICH/PCR	<i>Borrelia</i> Serology/PCR	Treatment	Follow-up
1	F/18	Multiple nodules in the trunk and arms, partial spontaneous regression. Clinical DDx: LyP?	Ig $\kappa$ + /IgH+	—/—	Excision, Doxycycline 2 $\times$ 100 mg for 2 wk	PR, AWD, 9 mo
2	F/13	Two closely opposed erythematous papules on the abdomen. Clinical DDx: Molluscum contagiosum?	Ig $\kappa$ + /IgH—	—/—	Excision	NED, 12 mo
3	M/17	6-year history of nodules on both arms and face	Ig $\lambda$ + /IgH+	—/—	Excision, intralesional IFN alpha (3 injections)	NED, 41 mo

AWD, alive with disease; DDx, differential diagnosis; ICH, immunohistochemistry; IFN, interferon alpha; LyP, lymphomatoid papulosis; NED, no evidence of disease; ND, not done; PCR, polymerase chain reaction.

**FIGURE 1.** Plaques on the left shoulder (A) and left arm (B) in patient 1.

### Histopathological, Immunohistochemical, and Molecular Biologic Data

Four specimens were available for the studies (2 biopsies were available from patient 2). In 3 specimens, there was a diffuse, nodular, or multinodular dermal infiltrate displaying lymphoid follicles with reactive germinal centers, either confluent or separated one from another (Figs. 3A, 4A). In the interfollicular infiltrate, small well-differentiated lymphocytes and lymphoid cells with clear cytoplasm were present

(Figs. 3B, 4B). Numerous plasma cells often forming collections at the periphery of the infiltrate were found (Fig. 4B).

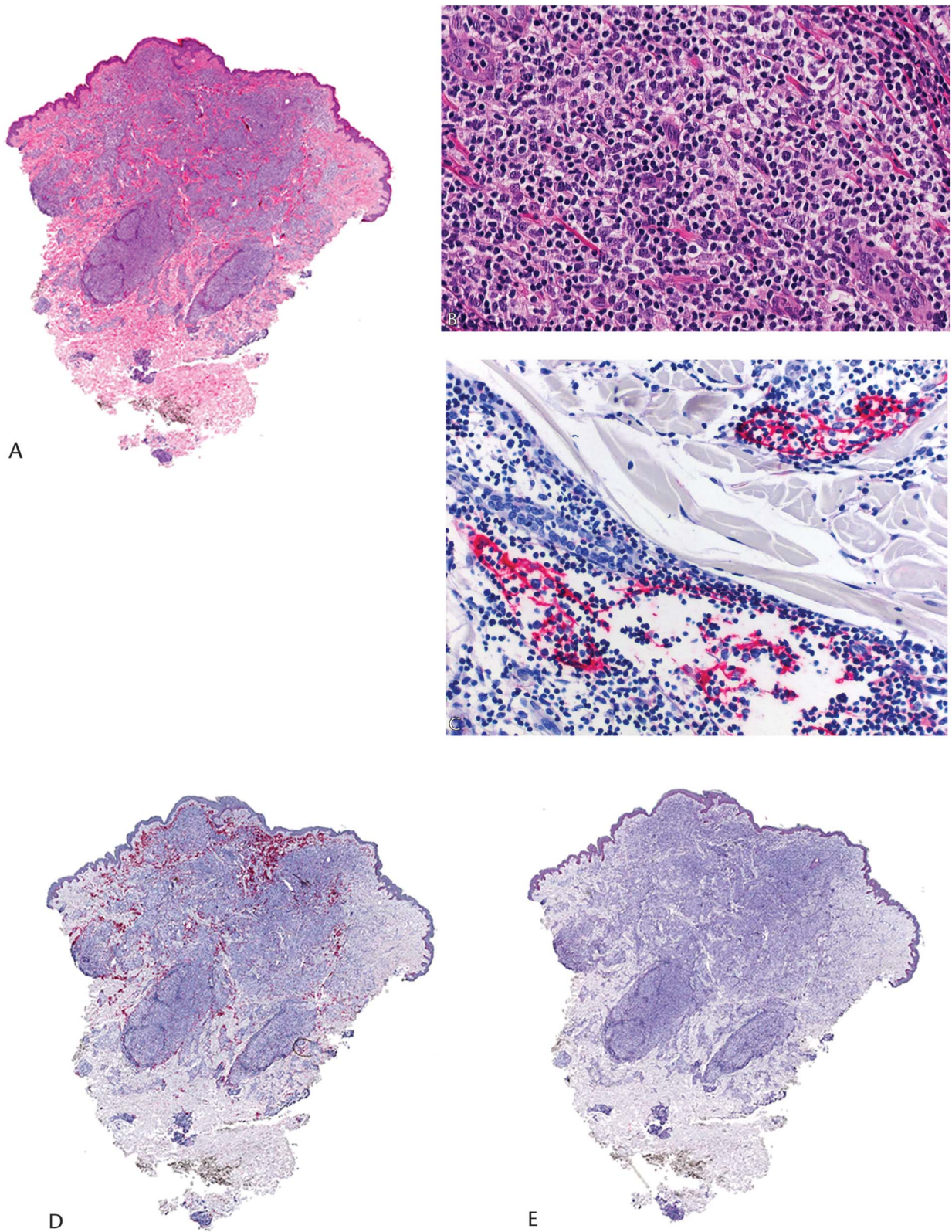
Overall, the infiltrate was predominantly composed of B cells (CD20, CD79a) with a variable number of reactive T cells (CD3) accounting for up to 30% of the infiltrate. The regular networks of follicular dendritic cells were highlighted by CD21 (Fig. 3C). As demonstrated by in situ hybridization, plasma cells were monotypic, with the restriction of the Ig lambda in case 3 (Figs. 3D, E), and Ig light chain kappa in cases 1 and 2 (kappa:lambda ratio 10:1 and 5:1, respectively) (Figs. 4C, D). IgG4 was negative in all 3 cases. In 2 cases, there were small collections of CD123-positive plasmacytoid dendritic cells.

The second specimen from patient 2 manifested a diffuse infiltrate composed almost exclusively of plasma cells admixed with few epithelioid histiocytes, focally forming small granulomas (Fig. 4B). Occasional multinucleated cells were present. At the periphery of the infiltrate, plasma cells were arranged in a single file pattern between somewhat thickened collagen fibers resembling a scar. The plasma cells manifested monoclonal restriction of the kappa light chain, as in the other specimen from this patient with a more conventional appearance of the lymphoma.

Monoclonal IgH rearrangement was found in 2 of the 3 studied specimens (cases 1 and 3). No *Borrelia burgdorferi* DNA was identified in all 3 cases studied by nested PCR. Serologic assays for *B. burgdorferi* was negative in all 3 patients (Table 1).

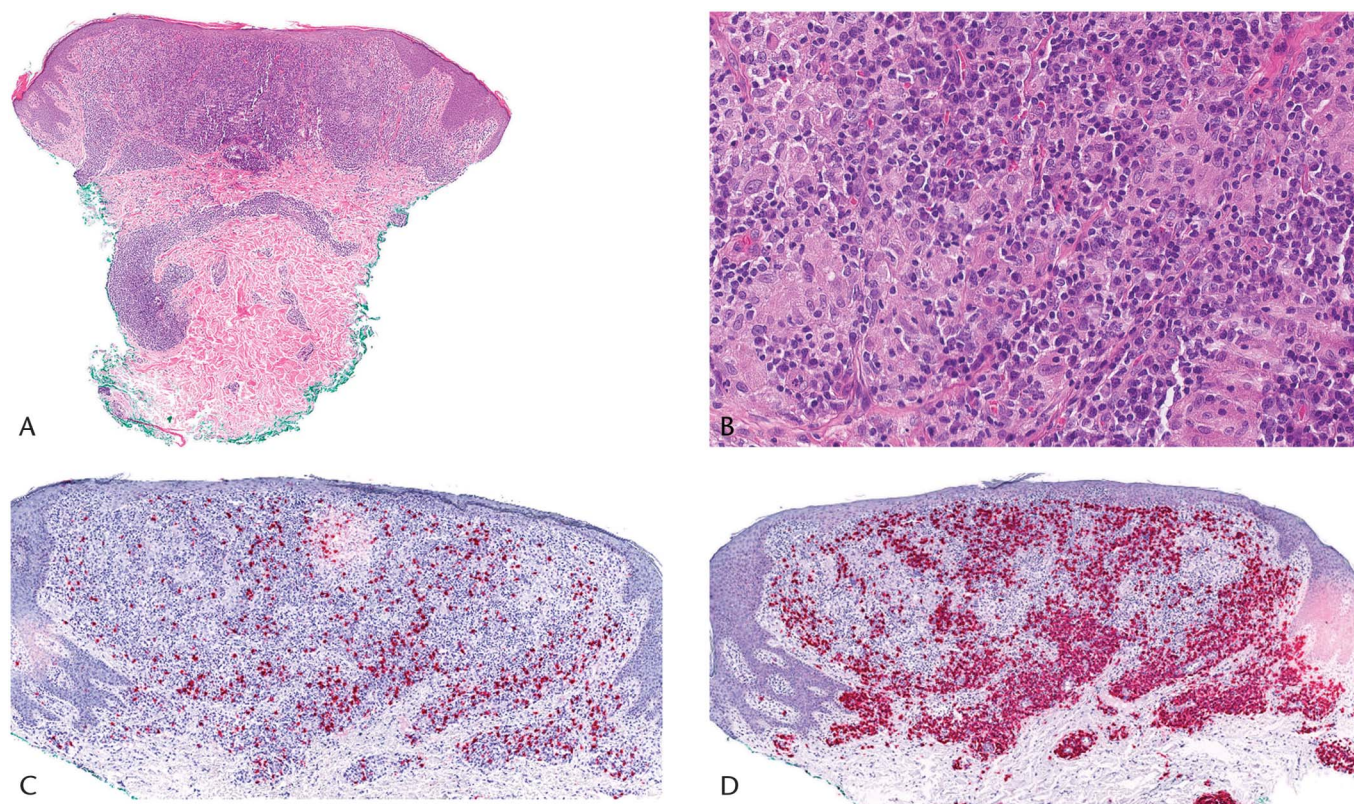
**FIGURE 2.** Nodular lesion on the chest in patient 3.





**FIGURE 3.** Multinodular infiltrate extending into the deep dermis (A) (H&E, magnification ×2.5). The infiltrate is composed of small lymphocytes, some with clear cytoplasm (B) (H&E, magnification ×200). Networks of CD21-positive follicular dendritic cells (C) (immunohistochemistry, magnification ×200). Expression of immunoglobulin light chains (D: lambda; E: kappa) with monoclonal expression of Ig light chain lambda (D) (in situ hybridization, magnification ×2.5).





**FIGURE 4.** Diffuse and nodular infiltrate predominantly in the upper and mid dermis (A) (H&E, magnification  $\times 2.5$ ). The infiltrate contains small lymphocytes, numerous plasma cells, and histiocytes (B) (H&E, magnification  $\times 200$ ). Expression of immunoglobulin light chains (C: lambda; D: kappa) with monoclonal expression of Ig light chain kappa (D) (in situ hybridization, magnification  $\times 25$ ).

## DISCUSSION

Primary cutaneous B-cell lymphomas rarely occur in children. Secondary cutaneous involvement by immature B-cell lymphoblastic lymphoma is not uncommon, whereas primary low-grade B-cell lymphoma, particularly PCMZL, is very rare in this age group. Fink-Puches et al,<sup>8</sup> who evaluated a series of 69 patients younger than 20 years with cutaneous lymphomas, found 7 patients with PCMZL (2 male and 5 female), with a mean age of 17 years (range, 12–20 years). Three cases of pediatric PCMZL (2 girls and 1 boy) have been reported by Amitay-Laish et al,<sup>9</sup> with all 3 patients manifesting multiple lesions. In 2 patients, the disease demonstrated a chronically relapsing course showing residual disease at 63 and 54 months of follow-up, respectively. An unusual clinical presentation with a 6-month history of waxing and waning erythematous papules on the limbs was reported by Sharon et al<sup>10</sup> in one of their 2 PCMZL cases. This 12-year-old boy was initially treated by oral doxycycline combined with topical 0.05% clobetasol cream but developed new lesions that were treated with topical nitrogen mustard. A similar treatment combined with surgical excision was chosen for the second patient of the authors.<sup>10</sup>

In addition to these small series, few pediatric cases of PCMZL were described as isolated case reports. Zambrano et al<sup>11</sup> documented a 14-year-old boy with a PCMZL on the lip. A case of pediatric PCMZL in an 11-year-old boy treated

with rituximab was described by Park et al.<sup>12</sup> Cozzio et al<sup>13</sup> used intralesional low-dose interferon  $\alpha 2$  for their 19-year-old male patient. Apparently, the first case of PCMZL from the USA has been documented by Sroa and Magro<sup>14</sup> who described a 15-year-old boy with one lesion. Dargent et al<sup>15</sup> reported an 11-year-old boy with PCMZL presenting with a solitary tumor on the head who was successfully treated by surgery alone. A trisomy 3 was detected on 14% of the neoplastic cells by FISH. Trisomy 3 is the most frequent chromosomal aberration seen in this type of lymphoma in adult patients, with approximately 20% of studied cases displaying this anomaly, either singly or in combination with t(14;18)(q32;q21) or t(3;14)(p14.1;q32).<sup>16–18</sup> Most recently, a 15-year-old boy with multiple lesions representing PCMZL and juxta-articular fibrotic nodules showing on histology nodular sclerosis with peripheral plasma cell-rich infiltrates or features reminiscent of quiescent lesions of chronic localized fibrosing leukocytoclastic vasculitis.<sup>19</sup> Remarkably, so far all pediatric patients with PCMZL were older than 10 years, ie, in the puberty or adolescence.

The differential diagnosis of PCMZL in children includes *Borrelia*-associated lymphocytoma cutis, which mostly affects the ear lobes, nipples, and scrotum in children and presents with a solitary lesion in most patients, which contrasts to the multifocal lesions in the majority of PCMZL.<sup>20,21</sup> The so-called lymphoplasmacytic plaque

usually favors the pretibial area.<sup>22–24</sup> Cutaneous plasmacytosis and plasmacytoma are also differential diagnostic consideration, although the latter is viewed in the current cutaneous lymphoma classifications as a variant of MZL.<sup>25,26</sup>

A subset of adult cases of PCMZL has been associated with *B. burgdorferi* infection in Europe, but not in the USA and Asia. With respect to pediatric cases, *B. burgdorferi* was identified by PCR in one of the 7 cases reported by Fink-Puches et al<sup>8</sup> and by indirect immunofluorescence and Western blot tests in the case described by Park et al.<sup>12</sup> In the patient reported by Ghatalia et al,<sup>19</sup> *Borrelia* PCR and serology were negative but immunohistochemistry using a modified method of focus-floating microscopy yielded spirochete-like forms. In our series, no association with *Borrelia* sp. was detected. Remarkably, in patient 1, a partial response to antibiotic treatment was observed indicating that other bacteria than *Borrelia* sp. may be involved in the pathogenesis of PCMZL.

Guitart and Gerami<sup>27</sup> suggested that some cases reported as PCMZL in children and young adults characterized by an indolent course with spontaneous remission and  $\lambda$  light-chain restriction may in fact represent marginal zone hyperplasia of the skin, a poorly defined condition at present analogous to atypical marginal zone hyperplasia of mucosa-associated lymphoid tissue (MALT) as found in the appendix and tonsils.<sup>28</sup> Although some lesions in our cases were small, suggesting an incipient disease, there was restriction of  $\kappa$  light chains.

Brenner et al<sup>29</sup> have recently demonstrated IgG4 expression in a significant subset of PCMZL with plasmacytic differentiation. None of the patients with IgG4 positive PCMZL had a preexisting systemic IgG4-related disease, suggesting a localized immunologic IgG4-driven process at an early stage of the disease. Interestingly, more than one third of their IgG4 cases demonstrated oligoclonal/polyclonal IgH rearrangement patterns. In none of our 3 cases tested were IgG4 cells present. This may be explained by a small study sample, but age-dependent differences cannot be totally discarded, because the study by Brenner et al<sup>29</sup> included only adult cases.

In conclusion, we have reported 3 pediatric cases of PCMZL. Taking into account the 20 heretofore published cases and our experience, it can be summarized that pediatric PCMZL show no gender predilection (12 male and 11 female), presents in approximately one third of cases (7/23) with lesions involving >1 anatomic site, and persistent disease occurs in a minority of instances (4/23). Association with *B. burgdorferi* is rare (4/23) but as with adult disease, geographic variation may be a factor. The course of pediatric PCMZL follows the indolent course and excellent prognosis as it is known from this lymphoma entity in adults.

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